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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/277,064	03/26/1999	LINDA A. SHERMAN	TSRI.433.1-D	3058

7590 11/06/2002

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/06/2002 21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/277,064	SHERMAN, LINDA A.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,13 and 25* is/are pending in the application.

4a) Of the above claim(s) *13 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Effective February 7, 1998; the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The request filed on 08/28/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No:09/277064 is acceptable and a CPA has been established. An action on the CPA follows.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claim 1 is being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claim 1 pertaining to lack of enablement for a method of specifically activating cytotoxic T lymphocytes *in vivo* in mice with a tumor expressing HER-2/Neu, wherein said cytotoxic T lymphocytes could target or kill tumor cells expressing HER-2/Neu *in vivo* remains for reasons already of record in paper No.15.

Applicant argues that the specification on pages 101-111 explicitly discloses that immunization of mice with the defined peptide results in the generation of cytotoxic T lymphocytes that specifically target malignant cells that express a Her-2/Neu protein.

Applicant's arguments set forth in paper No.20 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that this rejection only applies to the aspect of a method of specifically activating cytotoxic T lymphocytes in "mice with a tumor expressing HER-2/Neu", wherein "said cytotoxic T lymphocytes could target or kill tumor cells expressing HER-2/Neu *in vivo*".

It is further noted that the specification only discloses 1) generation of CTLs in mice without tumor burden, wherein the mice are HLA transgenic expressing HLA-A2 and CD8 molecules, 2) the claimed CTLs produced are xenogeneic and are produced by immunization of the mice with SEQ ID NO:12, and 3) the claimed CTLs produced kill tumor cell lines expressing A2.1 and Her-2/Neu *in vitro*. In addition, the specification discloses that since lysis by CTL is enhanced by preincubation with cytokine mixture, the tumor cell lines are not highly efficient in antigen presentation (specification, p.101-111, and page 106, lines 19-36).

The claim as written however encompasses a method of specifically activating cytotoxic T lymphocytes (CTLs) in an animal having a tumor burden that expresses a Her-2/Neu protein, wherein said cytotoxic T lymphocytes are not xenogeneic, and specifically target or kill *in vivo* primary malignant cells from a tumor that expresses a Her-2/Neu protein, the method comprising the step of immunizing with the peptide of SEQ ID NO:12 an animal that has a tumor burden that expresses a Her-2/Neu protein.

One could not extrapolate the teaching in the specification to the claim, because as discussed in previous Office action, in a situation where Her-2/neu is a self-protein,

such as in mice that have tumors that express HER/Neu, self-tolerance could eliminate T cells that are capable of recognizing Her-2/neu protein with high avidity. Thus unless tested, it is unpredictable that mice having tumors that express HER/Neu would produce CTLs specific for SEQ ID NO:12 with high affinity. Since the surviving CTLs would have low affinity to the claimed SEQ ID NO:12, one would not be able to predict that said CTLs with low affinity for SEQ ID NO:12 would be able to eliminate tumor cells *in vivo* (Sherman et al, of record, and the specification on page 101, lines 10-25). This inability of CTLs with low affinity to eliminate tumor cells *in vivo* would be even further exacerbated by tumors cells that either are not efficient in antigen presentation, similar to the tumor cell lines disclosed in the specification (p.106, lines 19-36), or tumor cells that do not express the specific tumor antigen due to an autochothonuous immune response (see discussion below, Cheever et al, of record, column 9, first paragraph). Further, as admitted by Applicant, after some period of time in the presence of tumor cells, T cells could lose their functional activity (specification, p.101). In addition, one could not extrapolate the *in vitro* tumor cell killing with *in vivo* tumor cell killing due to the following reasons: 1) Characteristics of tumor cell lines *in vitro* are different as compared to primary tumor cells (Freshney et al, Dermer et al, of record). Further, although *in vitro* a tumor cell line can express the peptide of SEQ ID NO:12 from Her-2/Neu protein, the expression of a Her-2/Neu, that is originally expressed with initiation of a tumor, could be subsequently lost, because an effective autochothonuous immune response can convert a Her-2/Neu positive tumor to Her-2/Neu negative (Cheever et al, of record, column 9, first paragraph). Thus it is unpredictable that mice with Her-2/Neu

tumor burden actually express or have adequate amount of Her-2/Neu protein on the tumor cell surface. Applicant however has not shown that in vivo primary tumor cells actually present or have adequate amount of the peptide of SEQ ID NO:12 on the cell surface, 2) I*n vitro* and *in vivo* environment is different, and 3) conditions for targeting tumor cells are different, wherein in *in vitro* the tumor cells are continuously exposed to the CTLs and in the presence of cytokines to increase the sensitivity of lysis by CTLs (Freshney et al, Dermer et al, of record). Further, as taught by Boon et al (of record), even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph). Thus it is unpredictable that cytotoxic T lymphocytes that are not xenogeneic would be activated in an animal with a tumor burden that expresses Her-2/neu; wherein said cytotoxic T lymphocytes could target or kill primary malignant cells that express a Her-2/Neu protein *in vivo*.

In summary, in view of the above discussion, and further in view of the unpredictability of tumor vaccination and anticancer drug discovery, as overwhelmingly evidenced by Ezzell et al, Spitler et al, Boon et al, Gura et al, Jain et al, Curti et al, and Hartwell et al (of record), it would have been undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 103, NEW REJECTION

Rejection under 35 USC 103 of claim 1 pertaining to obviousness over Grey et al, of record, in view of Cheever et al of record, Engleman et al, of record, and Yoshino, I et al, 1994, J Immunol, 152(5): 2393-400.

Claim 1 is drawn to a method of specifically activating cytotoxic T lymphocytes *in vivo*, wherein said cytotoxic T lymphocytes specifically target malignant cells that expresses a Her-2/Neu protein, the method comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:12.

Grey et al teach injection into transgenic mice putative CTL epitopes for inducing specific CTLs, and testing for lysis of peptide-coated target cell line Jurkat that expresses the A2 KB molecules (p. 76 and table 24). Grey et al also teach identification of immunogenic peptides, wherein one of the identified peptide is VMAGVGSPYV (p. 108, sixth sequence) which is from c-ERB2 (or Her-2/Neu), and has A2 binding affinity of 0.018 and which is exactly the same as the claimed SEQ ID NO:12 (Example 12 on page 79 and page 108, sixth sequence). Grey et al further teach that based the results on table 24, peptides that have a binding of at least 0.01 are capable of inducing CTLs (page 76, last paragraph).

Grey et al do not teach a method of specifically activating cytotoxic T lymphocytes *in vivo*, wherein said cytotoxic T lymphocytes specifically target malignant cells that expresses a Her-2/Neu protein.

Cheever et al teach peptides from p185 Her-2/Neu protein that are suitable for the CD8+ T cells response in individuals that are HLA-A2.1, which include SEQ ID

NO:29 (column 11, lines 23-36). SEQ ID NO:27 is exactly the same as the claimed SEQ ID NO:12.

Engleman et al teach that Jurkat cells are human leukemia cell lines (column3, second paragraph)

Yoshino et al teach tumor cell lines including the transfected cell lines that express HER2/Neu and assays for CTL-mediated lysis.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to use the method of inducing specific CTLs taught by Grey et al, using the peptide sequences taught by Grey et al or Cheever et al, one of which has exactly the same sequence as the claimed sequence of SEQ ID NO:12. It would have been obvious to test the lysis activity of the CTLs produced, using either peptide-coated malignant cell lines or cell lines transfected with and expressing said peptides including the peptide VMAGVGSPYV which is a Her-2/Neu protein, as taught by Grey et al, Cheever et al, and Yoshino et al, because these assays are routine in the art. One of ordinary skill in the art would have been motivated to produce specific CTLs *in vivo* with a reasonable expectation of success, because the peptide VMAGVGSPYV, which is from c-ERB2, has A2 binding affinity of 0.018, and peptides that have a binding of at least 0.01 are capable of inducing CTLs, as taught by Grey et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703)

305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

October 20, 2002

ANTHONY C. CAPUTA
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